A Review on the Update of Combined Hepatocellular Cholangiocarcinoma

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Abstract

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a primary liver tumor with neoplastic components of both hepatocytic and cholangiocytic differentiation. This unique neoplasm is gaining increasing recognition due to the intriguing pathology, tumor biology, and clinical behavior. It also poses challenges in diagnosis, treatment, and research, largely because of its histological and phenotypic diversity that lead to confusion in terminology and classification. There have been efforts attempting to unify the terminology of this neoplasm recently. Advances in investigation in various aspects have also been made. This review aims to update the terminology, classification, and clinical and pathological characteristics of cHCC-CCA.

Keywords
- combined hepatocellular carcinoma-cholangiocarcinoma
- hepatocytic
- cholangiocytic

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) is a heterogeneous primary liver tumor with many phenotypes that have common features of both hepatocytic and cholangiocytic differentiation. Clinically and radiologically, cHCC-CCA may mimic hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (iCCA). cHCC-CCA is gaining increasing attention clinically and pathologically, due to its unique biology, histopathology, and clinical behavior, as well as the difficulties in diagnosis, despite being rare (comprising ~1–5% of primary liver cancer).[1–4]

cHCC-CCA occurs in both cirrhotic and noncirrhotic liver, unlike in HCC and iCCA. HCC is frequently associated with cirrhosis, whereas cirrhosis is less common in iCCA.[5–7] The distinction between cHCC-CCA and HCC or iCCA is not always straightforward, largely due to the histological and phenotypic diversity of these tumors. It cannot be overemphasized that the heterogeneous nature of cHCC-CCA per se poses diagnostic challenges. In addition, the confusion in the terminology and the constantly revised classification of cHCC-CCA exacerbate the situation. All these may lead to clinical dilemma in treatment decision making and/or assessment of patient's prognosis.

A recent report by an international group of pathologists, radiologists, and clinicians who work in this field proposed a consensus terminology of primary liver carcinomas, with the aim of facilitating diagnosis, investigation, and management of this neoplasm by unifying the terminology.[8] In addition, the new World Health Organization (WHO) classification has revised the classification of cHCC-CCA, iCCA, and cholangiolocellular carcinoma (CLC) in its recently published Classification of Tumours of the Digestive System.[9]

We herein review the current clinical and pathological aspects of cHCC-CCA, including the updated WHO classification. Features of cHCC-CCA that may be confused with iCCA and HCC are also discussed. We hope this may provide clarification for practicing clinicians and pathologists to establish an appropriate diagnosis and therefore to choose the best possible treatment for the patient.

Historical Perspectives

cHCC-CCA was first described by Wells over a century ago,[10] using a case to illustrate this peculiar neoplasm. Wells also suggested cells derived from common embryology shared by

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hepatocytes and cholangiocytes as the origin of cHCC-CCA. This neoplasm, however, was not reviewed in detail until after nearly half a century by Allen and Lisa.[11] After three decades, Goodman et al published the first large series using immunohistochemistry to investigate 24 cases.[12] Both Allen and Lisa's and Goodman et al's studies classified these neoplasms into subtypes. Type 1 tumor designated by Allen and Lisa and type I tumor by Goodman et al were the collision-type tumor (separate HCC and CCA coincidentally found in the same liver) now not included in cHCC-CCA by the hepatopathology community including WHO.[9] The subtype with an intimate intermingling of HCC and CCA components, designated as type 3 tumor by Allen and Lisa[11] and defined by Goodman et al[12] as type II (transitional) neoplasms, are currently recognized as cHCC-CCA, and is the focus of discussion in this review.

Clinical and Epidemiological Considerations

Majority of the intimately intermingled type tumors in the studies by Allen and Lisa[11] and Goodman et al[12] arose in the background of cirrhosis. While subsequent investigations also found cHCC-CCA that usually arises in patients who have underlying liver disease and advanced fibrosis,[13,14] it may also arise in noncirrhotic liver, and cirrhosis is not necessary for cHCC-CCA to occur. The prevalence of background cirrhosis in cHCC-CCA is variable, depending on data derived from different regions or patient populations, or criteria used for the diagnosis of cHCC-CCA.[7,15] Similarly, the underlying etiology of liver disease, such as viral hepatitis B or C, is also variable among different reports. This may be at least partially attributed to the different geographic regions and diagnostic criteria used in each study. Cases of cHCC-CCA occurring in patients after tumor treatment such as transarterial chemoembolization have been recently observed with increasing awareness among investigators[16,17]

Current Status and Challenges of cHCC-CCA

Histologically, cHCC-CCA is characterized as a primary liver tumor comprising both hepatocytic and cholangiocytic differentiation in the same tumor (►**Fig. 1A, B**). These different components show transitional features; hence, cHCC-CCA differs from collision tumors, which contain separate HCC and CCA without transitional features. Importantly, in cHCC-CCA, these two different components exist in the tumor with varying proportions, tumor differentiation and grades, and morphological diversity. Therefore, most, if not all forms of cHCC-CCA, may show histological features of some other forms. As a result, such tumor heterogeneity leads to diagnostic challenges. Radiographically, proportion of the HCC and CCA components in cHCC-CCA generally reflects the imaging features: cHCC-CCA with a predominant HCC component mimics HCC radiographically,[18,19] whereas cHCC-CCA with a predominant CCA component resembles CCA radiographically.[18] On the other hand, tumor differentiation, grade and morphological diversity have a great impact on the pathological interpretation.

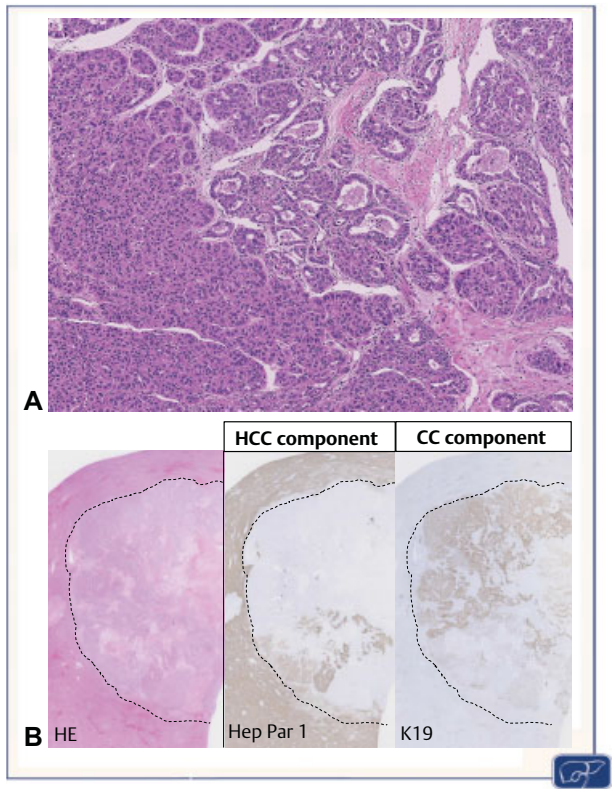

Fig. 1 Combined hepatocellular cholangiocarcinoma (cHCC-CCA). (**A**) Hematoxylin and eosin stain shows two different cancer components, HCC with a thick trabecular appearance (left) and CCA with glandular structures embedded in desmoplastic stroma (right), intimately interdigitating with each other at transitional region. Two different components are highlighted by immunohistochemistry. (**B**) HCC component is positive for hepatocytic marker such as Hep Par 1. In contrast, CC component is positive for K19, which is a biliary marker.

The so-called typical cHCC-CCA, a tumor composed of both unequivocal HCC and iCCA components with a transitional area where these two components intimately intermingle with each other, accounts for around 17% of cases.[20] The remaining cases show heterogeneity with different tumor structures, such as trabecular, glandular, ductular reaction-like, cord-like, and solid, as well as tumor differentiation (►**Fig. 2**). One should note that ductular configuration is often seen in CLC, just as cord-like tumor structure is observed in intermediate cell carcinoma. In fact, the recent WHO classification requires ductular reaction-like structure greater than 80% to be called CLC. Importantly, ductular configuration and cord-like structure are predominant and main tumor elements in CLC and intermediate carcinoma, respectively, but not just a portion of the histological spectrum. CLC and intermediate carcinoma will be discussed in detail in the later sections.

Tumor differentiation also varies and immunohistochemistry, while not necessary, is often used to confirm hepatocytic and cholangiocytic differentiations. All these underscore the challenges of cHCC-CCA that present unique features that lead to the difficulty in standardizing pathological diagnostic criteria and terminology as well as reaching agreement in diagnosis among pathologists.

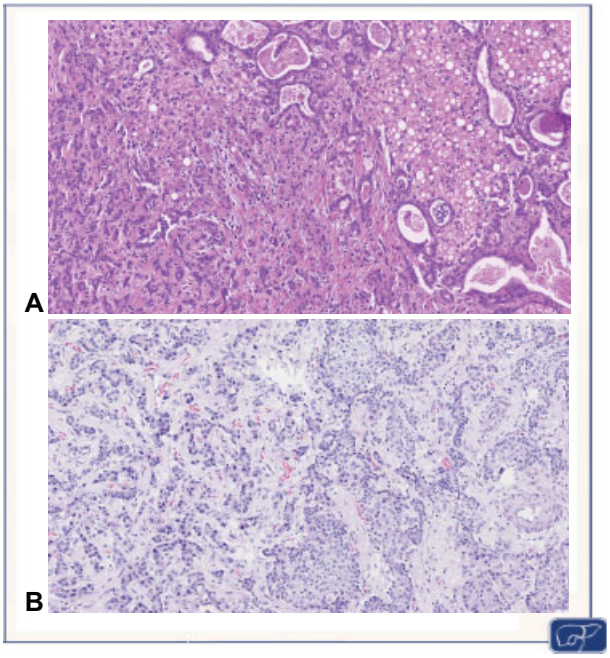

Fig. 2 Histological diversity in combined hepatocellular cholangiocarcinoma (cHCC-CCA) shows histological diversity comprising different components (**A**: ductular configuration, HCC, and iCCA. **B**: ductular configuration and HCC)

Indeed, WHO classification, a standardized pathological diagnostic criteria used worldwide, takes on the task to adapt the definition of cHCC-CCA in each new edition. In brief, the previous 4th edition published in 2010[21] subdivided cHCC-CCA into classical cHCC-CCA or cHCC-CCA with stem cell features (three subtypes: typical, intermediate-cell, and cholangiolocellular), whereas the latest (5th) edition[9] published in 2019 omits the subcategorization and it is solely defined as a primary liver carcinoma with unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumor, which is exactly the same as the definition in the 3rd edition published in 2000. This change was largely due to the fact that "stem cells" may potentially be found in all forms of cHCC-CCA. In addition, there has not been prognostic impact among these subtypes.[20,22,23] An international consensus paper[8] recently published also stated that it is not necessary to subtype cHCC-CCA, but recommended mentioning "stem/progenitor cell features present" in the comments, when it is observed.

Finally, it is worth mentioning that while several earlier classification systems, such as Allen and Lisa's classification[11] and Goodman et al's classification[12] deserve historical merit, some of the tumors classified as cHCC-CCAs using these systems would not be considered cHCC-CCA in the current classification system.[11,12,24]

Use of Immunohistochemistry

Identifying both hepatocytic and cholangiocytic differentiation is essential for the diagnosis of cHCC-CCA. The recent consensus paper recommends that immunohistochemistry is not prerequisite for the diagnosis of cHCC-CCA,[8] while morphology is the key. Nevertheless, there are occasions that it is not straightforward to assess hepatocytic and cholangiocytic differentiation using only hematoxylin and eosin and histochemical (for matrix protein and mucin) stains. For instance, poorly differentiated cholangiocarcinoma will show cord-like structure without mucin production that needs to be differentiated from poorly differentiated HCC or ductular configuration seen in CLC or intermediate cell carcinoma. It is important to note the ultimate goal is to make a correct diagnosis for the most appropriate management and the subsequent molecular and clinical studies. Immunohistochemistry that can be useful to confirm hepatocytic and/or cholangiocytic differentiation is summarized in ►**Table 1**. It is important that these antibodies need to be used and interpreted prudently by an experienced pathologist, who is familiar with their sensitivities and specificities, with the tumor morphology in hematoxylin and eosin as the gold standard in diagnosis.

For example, hepatocytic differentiation can be confirmed by one of these markers: cytoplasmic expression by Hep Par 1 (►**Fig. 1B**), Arginase-1 and/or canalicular expression by CD10, polyclonal CEA, and/or bile salt export pump. Cholangiocytic differentiation can be assessed with keratin 19 or epithelial membrane antigen (EMA) (►**Fig. 1B**).

Table 1 Immunohistochemical markers for hepatocytic and cholangiocytic differentiation

Immunohistochemical markers	Pattern of immunoreactivity	Remarks
Hepatocytic differentiation		
Hep Par 1	Cytoplasmic positivity	It can be negative in poorly dif. HCC
Arginase-1	Cytoplasmic positivity	It can be negative in poorly dif. HCC
Polyclonal CEA	Canalicular positivity	It often shows background staining
CD10	Canalicular positivity	
Bile salt export pump	Canalicular positivity	It can be negative in poorly dif. HCC
Cholangiocytic differentiation		
Cytokeratin 19	Cytoplasmic positivity	Membranous positivity is suggestive of K19 pos. HCC
EMA	Cytoplasmic/apical positivity	Cytoplasmic positivity: large duct type iCCA Apical expression: small duct type iCCA/CLC

Abbreviations: CEA, carcinoembryonic antigen; CLC, cholangiolocellular carcinoma; dif, differentiation; EMA, epithelial membrane antigen; HCC, hepatocellular cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma.

Diagnostic Pitfalls

Respective sensitivities and specificities of the several hepatocytic markers listed in ►**Table 1** vary, raising the possibilities that the differences in the diagnosis and tumor classification of cHCC-CCA in various studies might have attributed to different antibodies used. Standardization of using markers for hepatocytic differentiation may be helpful in establishing the diagnosis. Another important point to keep in mind is that the presence of various putative immunohistochemical markers for stem cells in HCC should not lead to overdiagnosis of cHCC-CCA. For instance, a substantial number of HCCs demonstrate K7 expression, which is known as a biliary marker.[25,26]

Therefore, assessing morphological features should always take priority to avoid overinterpreting immunohistochemical staining for diagnosis.

Differential Diagnosis of cHCC-CCA with K19 Positive HCC

Keratin 19 positive HCC (K19 pos-HCC) is different from cHCC-CCA, as K19 pos-HCC is a pure HCC without any glandular structure. In addition, the patterns of immunoreactivity of K19 are different between K19 pos-HCC and cHCC-CCA. Briefly, K19 pos-HCC shows a weak and membranous K19 positivity with variable intensity. In contrast, K19 shows a relatively monotonous cytoplasmic expression in the cholangiocarcinoma component of cHCC-CCA.[27] The distinction is important as their prognoses are different.

Cholangiolocellular Carcinoma (►Fig. 3)

CLC was first reported by Steiner and Higginson in 1959 as a primary liver cancer characterized by cholangioles-like cord structure and ductular reaction-like anastomosing glands with abundant fibrous stroma.[28] They also described that some cases of CLC contained HCC-like features, suggesting "junctional potentialities."[28]

The latest WHO classification clearly defines CLC as a tumor comprising more than 80% of ductular reaction-like structure, resembling a ductular reaction in chronic liver disease (►**Fig. 3A**).[29] At the periphery, CLC may show "replacing growth pattern" resembling HCC[30] (►**Fig. 3B**). CLC may also contain HCC-like structures in the tumor, located at the periphery (►**Fig. 3C**).[29] It may also coexist with an iCCA component, mainly located in the center of the tumor. However, the predominant tumor structure of CLC is a ductular configuration, which is the main difference from cHCC-CCA.

Clinically, CLC is often misdiagnosed as HCC as it is a mass-forming tumor with hypervascularity and associated with chronic liver diseases.[27,29] In addition, CLC has a better prognosis than iCCA.[29,31] Therefore, CLC should be recognized as being different from HCC or iCCA. As of the 5th WHO classification, CLC is categorized as either cHCC-CCA or small-duct iCCA based on the presence of hepatocytic differentiation: if hepatocytic differentiation is present in CLC, it is categorized as cHCC-CCA. Without hepatocytic differentiation, it is classified as small-duct iCCA. This is largely due to the fact that genomic profiles are different in CLC depending on the presence of hepatocytic differentiation. Briefly, CLC without hepatocytic differentiation shares immunohistochemical characteristics and genomic profiles with iCCA.[32–34] In contrast, CLC with hepatocytic differentiation shares a similar genomic status with cHCC-CCA (e.g., PBRM1 mutation and alteration of AR1D1[32]). This indicates that the identification of hepatocytic differentiation in CLC is essential not only for the diagnosis but also for proper molecular assessment.

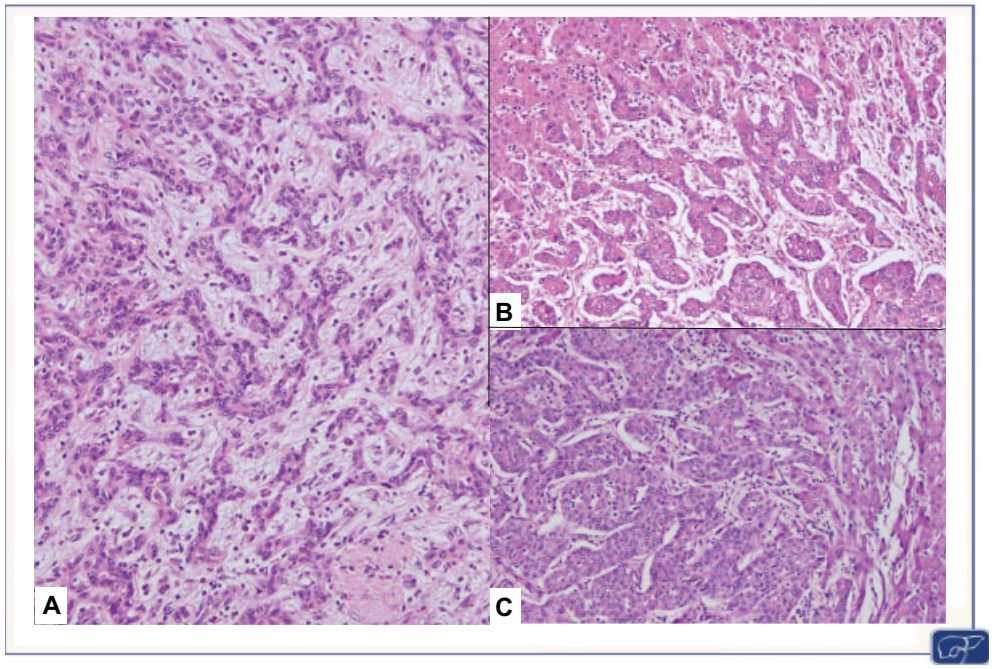

Fig. 3 Cholangiolocellular carcinoma. Tumor shows ductular reaction-like tumor structure associated with fibro-inflammatory stroma (**A**). Tumor shows a replacing growth pattern in periphery (**B**). Hepatocytic differentiation is also noticed (**C**).

Intermediate Cell Carcinoma

Unlike the previous WHO classification, intermediate cell carcinoma is now separately described as a unique primary liver tumor in the recently published consensus paper and the new WHO classification. It is characterized as a tumor showing strands or trabeculae of small, uniform, round-to-oval cells with scant cytoplasm and hyperchromatic nuclei in a background of thick desmoplastic stroma.[35] Mucin production is not seen. The majority of cases show either chronic hepatitis or cirrhosis in the background. Immunohistochemically, the tumor cells show simultaneous immunoreactivities by both hepatocytic and cholangiocytic markers, which might have attributed to being called cHCC-CCA in many occasions. A diagnosis of intermediate cell carcinoma is reserved for only the entire tumor containing a pure population of cells with the above features.

Molecular Profiles (►Table 2)

Just as the histological aspects in cHCC-CCA vary, so does the molecular profile.[31,32,34,36–42] Previous studies found that the genetics of cHCC-CCA were closer to iCCA than HCC.[42] However, the recent study performed by Joseph et al showed that the genetics of cHCC-CCA, classical type, are distinct from iCCA but similar to HCC, for example, alterations in TERT, TP53, cell cycle genes (CCND1, CCNE1, CDKN2A), receptor tyrosine kinase/Ras/PI3-kinase pathway genes (MET, ERBB2, KRAS, PTEN). In contrast, alterations in IDH1, IDH2, FGFR2, or BAP1, which are often seen in iCCA, were not identified.[36] Moeini et al described the different genomic status of cHCC-CCA depending on their subtypes.[34] In brief, cHCC-CCA composed of clear HCC and iCCA components showed TP53 mutation and TERT promoter like in HCC and iCCA. In contrast, cHCC-CCA with stem-cell type showed enrichment of progenitor-like signatures, activation of specific oncogene pathways such as MYC and IGF, and signatures related to a poor clinical outcome.

Variations in the results of molecular profiles in cHCC-CCA may be attributed to the different predominant tissues in the areas sampled or to the different pathological criteria used. It is highly critical for investigators to study tumor cell population using a well-defined classification to best characterize its molecular signature.

Tumor Staging

cHCC-CCAs are staged in the current AJCC system using the cholangiocarcinoma protocol.[43] However, this categorization poses problems, especially in clinical decision making for the management and prediction of prognosis. Biologically, these tumors are sufficiently distinct from both hepatocellular carcinoma and cholangiocarcinoma that a unique staging system may need to be designated in the future.

Treatment

Surgical resection remains the only treatment of choice to potentially cure localized cHCC-CCA. Recently, several groups have also proposed liver transplantation as a treatment option, based on the data suggesting the prognosis of patients undergoing liver transplantation with cHCC-CCA was comparable to that of patients undergoing liver resection.[23,44,45] However, these studies were limited by their retrospective nature. Therefore, introducing liver transplantation as a treatment option for cHCC-CC needs to be considered prudently, including the risk of lifelong immunosuppression and the scarcity of donor liver. Prospective studies are needed with all benefits and risks cautiously and objectively evaluated.

Chemotherapy may cause some treatment response; however, it does not prolong patient's survival. Due to its rarity and the lack of clearly defined diagnostic criteria in the past, there are no standard systemic or locoregional therapies such as transarterial chemoembolization or external beam radiation therapy for recurrent or metastatic cHCC-CCA,[46,47] which

Table 2 Summary of published molecular profiles of cHCC-CCA

Authors	Year	Technique	No.	Molecular features
Sasaki et al[32]	2019	Direct sequence	48	TERT, ARID1A, PBRM1, ARID2, BAP1, p53, KRAS, IDH1/2
Joseph et al[36]	2019	Capture-based NGS	20	TERT, TP53, CCND1, CCNE1, CDKN2A, MET, ERBB2, KRAS, PTEN, ARID1A, ARID2, CTNNB1, AXIN, APC
Liu et al[37]	2018	WGS, WES, and RNA-seq	10	TP53, CTNNB1, RYR3, FBN2, KCNN3
Wang et al[38]	2018	WES	7	VCAN, ACVR21, FCGBP
Jeon et. al[39]	2018	Capture-based NGS	4	TP53, PTEN, MET, c-MYC, CDK6, CTNNB1, CCND1
Sasaki et al[40]	2017	Direct sequence	53	KRAS, IDH1/2, ARID1A, TERT
Chen et al[31]	2017	Direct sequence	23	IDH1/2
Moeini et al[34]	2017	GEP, copy number variation, WES	18	TP53, TERT, IDH1/2, Chromosomal instability, MYC, IGF2, mTOR,
Coulouarn et al[41]	2012	GEP	20	RRA9, TGFB3, TGFB2, SMURF2, VDR, TGIF1, INHBA, SFRP4, CDH1, MMP7, PPP2R3A, RARB. CD44, FZD6, AKT3, LEF1
Cazals-Hatem-D et al[42]	2004	LOH	15	TP53, chromosome instability

Abbreviations: cHCC, combined hepatocellular-cholangiocarcinoma; GEP, gene-expression profiling; LOH, loss of heterozygosity; NSG, next-generation sequencing; WES, whole exome sequencing; WGS, whole genome sequencing.

await further investigation. Similarly, until now, data of immunotherapy treating cHCC-CCA are also lacking, and future studies are warranted.

Future Perspectives

To date, the outcome of cHCC-CCA patients undergoing liver transplantation and the roles of potential target therapies in the era of precision medicine remain unclear. Further investigation, including prospective clinical trials, basic research, and translational studies, is warranted. To achieve this, collaborative efforts among researchers, hepatologists, surgeons, oncologists, radiologists, and pathologists will be necessary. The recent published consensus paper on the terminology of cHCC-CCA[8] and the updated WHO classification[9] provide the groundwork for ongoing and future research with more stringent classification of these tumors, some of which may have been previously erroneously categorized leading to controversial data. Nevertheless, concordance among investigators in diagnosing cHCC-CCA using updated diagnostic criteria needs to be tested and validated. Standardization of the pathological diagnosis of primary liver tumors, including cHCC-CCA and CLC, and improvement in the diagnostic concordances among pathologists based on the consensus paper are currently in progress.[8] Finally, standardization of identification of hepatocytic differentiation is warranted to diagnose and categorize the tumor concordantly. Only when this is achieved can molecular investigations unravel the genetic profiles and signaling pathways.

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Conflicts of Interest
Both authors have no conflicts of interest to declare.

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